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Abstract: Nicotine has been proposed to be a cognitive enhancer, particularly in schizophrenia patients. So far, the published studies of nicotine effects on antisaccade performance in schizophrenia patients only tested participants who were deprived smokers. Thus, we aimed to test both smoking and non-smoking patients as well as healthy controls in order to extend previous findings. Moreover, we employed a paradigm using standard and delayed trials. We hypothesized that, if nicotine is a genuine cognitive enhancer, its administration would improve antisaccade performance both in smoking and non-smoking participants. A total of 22 patients with schizophrenia (12 smokers and 10 non-smokers) and 26 controls (14 smokers and 12 non-smokers) completed the study. The effects of a nicotine patch (14 mg for smokers, 7 mg for non-smokers) on antisaccade performance were tested in a randomized, double-blind, placebo-controlled, cross-over trial. Schizophrenia patients made significantly more antisaccade errors than controls ($p = 0.03$). Both patients and controls made fewer antisaccade errors in the delayed trials than in the standard trials ($p < 0.0001$). Nicotine significantly reduced antisaccade error rate in the standard trials, but not in the delayed trials ($p = 0.02$). Smoking status did not influence the nicotine effect on antisaccade error rate ($p = 0.10$) indicating an equal procognitive effect of nicotine in smokers and non-smokers. Overall the present findings indicate that beneficial effects of nicotine on antisaccade performance are not confined to smoking schizophrenia patients. Instead, the findings likely represent genuine nicotine-induced enhancement of cognitive performance.

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ARTICLE

Nicotine enhances antisaccade performance in schizophrenia patients and healthy controls

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Abstract

Nicotine has been proposed to be a cognitive enhancer, particularly in schizophrenia patients. So far, the published studies of nicotine effects on antisaccade performance in schizophrenia patients only tested participants who were deprived smokers. Thus, we aimed to test both smoking and non-smoking patients as well as healthy controls in order to extend previous findings. Moreover, we employed a paradigm using standard and delayed trials. We hypothesized that, if nicotine is a genuine cognitive enhancer, its administration would improve antisaccade performance both in smoking and non-smoking participants. A total of 22 patients with schizophrenia (12 smokers and 10 non-smokers) and 26 controls (14 smokers and 12 non-smokers) completed the study. The effects of a nicotine patch (14 mg for smokers, 7 mg for non-smokers) on antisaccade performance were tested in a randomized, double-blind, placebo-controlled, cross-over trial. Schizophrenia patients made significantly more antisaccade errors than controls ($p=0.03$). Both patients and controls made fewer antisaccade errors in the delayed trials than in the standard trials ($p<0.0001$). Nicotine significantly reduced antisaccade error rate in the standard trials, but not in the delayed trials ($p=0.02$). Smoking status did not influence the nicotine effect on antisaccade error rate ($p=0.10$) indicating an equal procognitive effect of nicotine in smokers and non-smokers. Overall the present findings indicate that beneficial effects of nicotine on antisaccade performance are not confined to smoking schizophrenia patients. Instead, the findings likely represent genuine nicotine-induced enhancement of cognitive performance.

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Key words: Antisaccade, executive function, nicotine, nicotinic acetylcholine receptor, schizophrenia.

Introduction

The antisaccade task (Hallett 1978) represents a relatively simple paradigm, which serves as a model system for an important aspect of executive control (Reuter and Kathmann, 2004; Hutton and Ettinger, 2006). This task demands the inhibition of an automatic, phylogenetically old and ontogenetically over-learned saccade towards a peripheral stimulus; instead, the participant has to initiate a voluntary eye movement to the mirror image location of the stimulus. The ability to control behaviour flexibly, responding automatically to stimuli in one situation and suppressing this automatic response in favour of an alternative response in a different situation, is one of the key components of executive control. Patients with schizophrenia, their unaffected-first degree relatives and individuals with schizophrenia spectrum disorders exhibit impaired antisaccade performance reflected by increased antisaccade error rates, increased antisaccade latencies and also inaccurate antisaccade amplitudes (i.e. impaired antisaccade spatial gain; Clementz et al., 1994; Ross et al., 1998; McDowell et al., 1999; Ettinger et al., 2004, 2006; Maccabe et al., 2005; Hutton and Ettinger, 2006; Nieman et al., 2007; Petrovsky et al., 2009).

Two antisaccade studies with schizophrenia patients employed a delayed antisaccade paradigm in addition to the commonly used standard paradigm (Reuter et al., 2005, 2007): in those studies the participants performed antisaccade tasks that required the execution of a voluntary saccade immediately after the onset of a peripheral visual stimulus (standard antisaccades) or after a brief delay (delayed antisaccades). In the delayed condition, participants have to continue to fixate on a central stimulus until they are prompted to perform the antisaccade. One of the main findings in both studies was that, regardless of condition, schizophrenia patients made more antisaccade errors than controls.

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Furthermore, antisaccade error rate was reduced in the delay conditions compared to the standard condition (Reuter et al., 2005, 2007). Thus, the results of Reuter et al. (2005, 2007) suggest that schizophrenia patients may have a specific deficit in initiating voluntary saccades and that this deficit is at least in part responsible for the antisaccade deficit.

It has been shown previously that antisaccade performance is sensitive to cholinergic manipulation. Nicotine enhanced antisaccade performance in studies with schizophrenia patients (Depatie et al., 2002; Larrison-Faucher et al., 2004) and in healthy participants (Depatie et al., 2002; Rycroft et al., 2006, 2007; Dawkins et al., 2007; Ettinger et al., 2009; Bowling and Donnelly, 2010; Petrovsky et al., 2012), while the anticholinergic substance procyclidine worsened antisaccade performance in schizophrenia patients (Ettinger et al., 2003). In addition, varenicline [a relatively specific $\alpha4\beta2$ nicotinic acetylcholine receptor (nAChR) agonist] improved antisaccade performance in schizophrenia patients in a recent clinical trial (Hong et al., 2011). However, the only two published studies of nicotine effects on antisaccade performance in schizophrenia patients (Depatie et al., 2002; Larrison-Faucher et al., 2004) tested deprived smokers. Methodologically, testing deprived smokers is not optimal, because it is difficult to determine whether performance-enhancing effects of nicotine represent genuine enhancement or simply a relief-from-withdrawal phenomenon (Heishman et al., 2010).

It remains to be elucidated by which mechanisms nicotine exerts its beneficial effects on antisaccade performance. A paradigm involving standard and delayed antisaccades might at least disentangle two components of antisaccade performance: inhibition and voluntary saccade generation. In standard trials both inhibition of a reflexive saccade and volitional saccade generation are required simultaneously, whereas in delayed trials inhibition is facilitated due to elongated fixation and saccade generation is required after the temporal delay. Assuming that nicotine enhances inhibitory processes (possibly via higher order cognitive functions such as strengthened working memory representations supporting goal-directed activity; Rycroft et al., 2007), we would expect that nicotine would be more beneficial in standard antisaccade trials than in delayed trials.

In the present study, therefore, we aimed at testing the effects of nicotine on antisaccade performance both in deprived smokers and in non-smokers with and without schizophrenia in order to: (1) replicate the findings on nicotine in deprived smokers with schizophrenia; (2) extend the design to non-smoking schizophrenia patients. A performance-enhancing effect of nicotine only in deprived smokers would imply a relief-from-withdrawal phenomenon, whereas an equal performance-enhancing effect of nicotine both in smokers and non-smokers would indicate genuine performance enhancement by nicotine instead of simple relief-from-withdrawal. Thus, the combined assessment of samples of smokers and non-smokers offers the advantage of distinguishing between withdrawal relief and cognitive enhancement. Moreover, we used the variation of the antisaccade task as employed by Reuter et al. (2005, 2007) in order to investigate nicotine effects in standard antisaccades and delayed antisaccades.

Thus, we hypothesized: (1) patients with schizophrenia will exhibit worse antisaccade performance than controls; (2) antisaccade errors will be less frequent in the delayed antisaccade task than in the standard task; (3) nicotine administration will improve antisaccade performance both in smoking and non-smoking participants; (4) nicotine will improve standard antisaccades to a greater extent than delayed antisaccades.

Method and materials

Participants

Male and female participants, smokers as well as non-smokers, aged 18–55 yr were included in the present study. Patients with a diagnosis of either 'schizophrenia, paranoid type' (DSM-IV 295.3) or of 'schizo-affective disorder' (DSM-IV 295.7) were included. Participants with psychosis were recruited from the out-patient clinic of the University Hospital, Bonn. Control participants were recruited from the local community by advertisement and by contacting a random sample of the inhabitants of Bonn based on a list from the city registry. For control participants it was a requirement that they did not have a relative with a history of psychosis (i.e. schizophrenia, schizo-affective disorder, bipolar disorder) up to the third degree of kinship. All participants were interviewed with the German version of the Structured Clinical Interview (SCID-I) for DSM-IV (Wittchen et al., 1997). SCID-I verified diagnosis in patients with psychosis and ensured control participants were free from a current or lifetime Axis I disorder. In patients, current symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Calgary Depression Scale for Schizophrenia (Muller et al., 1999). Non-smoking participants were defined as individuals who had smoked $\leqslant$100 cigarettes during their lifetime (Schoenborn et al., 2003). Verbal IQ of all participants was estimated with a standardized German vocabulary test, the Mehrfachwahl-Wortschatz-Intelligenztest-B (Lehrl, 1989).

Exclusion criteria were: head injury with loss of consciousness >5 min; lifetime history of alcohol or substance abuse or dependence; history of neurological illness or another severe medical condition. Additional exclusion criteria for patients were: clinical instability; recent change in medication (<6 wk); anticholinergic medication. Further exclusion criteria were severe obesity (BMI >35 kg/m^2) and uncorrected visual impairments. Furthermore, the following exclusion criteria were

employed in order to avoid serious side-effects caused by the nicotine application: cardiovascular disease; hypertension; atopic or eczematous dermatitis (due to localized patch sensitivity); severe renal or hepatic impairment or active peptic ulcers; hyperthyroidism; pheochromocytoma; insulin-dependent diabetes; hypersensitivity to patches; hypersensitivity to nicotine or any of the ingredients of the patches. A study physician ensured that all inclusion and exclusion criteria were met. Approval of the local ethics committee and the German Federal Institute for Drugs and Medical Devices was obtained and the study was registered with http://www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01315002). Participants provided written informed consent before inclusion. All participants were compensated for their participation.

Procedures

On both testing days, a urine drug screening test (nal von minden, Germany) was applied before patch application to ensure participants had abstained from amphetamine, benzodiazepine, cocaine, THC cannabinoides and opiate/morphine. All female participants additionally underwent a urine pregnancy test (Hitado hCG; Hitado Direkt, Germany) on both testing days to confirm they were not pregnant. In smokers, smoking abstinence (12 h before patch application) was verified by measuring breath carbon monoxide (<10 ppm).

Nicotine was administered in a randomized, double-blind, placebo-controlled, cross-over design. Each participant completed two oculomotor testing sessions (one nicotine session and one placebo session; the order of sessions was counterbalanced). Nicotine was applied via patches (NiQuitin Clear; GlaxoSmithKline, UK; 7 mg patch for non-smoking participants, 14 mg patch for smoking participants). The nicotine dosages were chosen in accordance with previously published studies which found cognitive effects of nicotine in the absence of significant side-effects (Levin et al., 1998; Depatie et al., 2002; Poltavski and Petros, 2006; Petrovsky et al., 2012). Placebo patches (Fink and Walter GmbH, Germany) of similar appearance were applied. Both patches were applied non-visibly to the upper back of the participant by a research assistant who was not running the test sessions, in order to ensure double-blindness. Oculomotor testing commenced 3 h after patch application. Nicotine administration using the NiQuitin patch generates a fast-rising nicotine plasma level (a nicotine plateau level is achieved 2–4 h after application according to the summary of product characteristics of NiQuitin Clear).

Cotinine plasma levels

Blood samples were collected in anticoagulant EDTA 9 ml tubes and centrifuged for 10 min with a centrifugal force of 1610 ***g***. Plasma was collected, allotted to two aliquots and frozen at $-80\ ^{\circ}$C in order to be later analysed for cotinine. Cotinine was quantified with liquid chromatography–mass spectrometry, a highly specific and sensitive method (Gabr et al., 2011).

Saccadic tasks

Participants were seated 41 cm from a 17-inch monitor; head movements were minimized using a chinrest. The testing room was quiet and dimly lit. Experimental stimuli were presented using ERTS® (BeriSoft Corporation, Germany). Participants performed one block of intermixed standard and delayed prosaccade trials and one block of intermixed standard and delayed antisaccade trials. The order was fixed beginning with the block of prosaccades.

A standard trial (i.e. a trial with no delay) started with the fixation of a central white cross on a black background for the duration of 1000, 1500, 2000 or 2500 ms at random. Subsequently, a 440 Hz sine wave tone (50 ms) and a peripheral target dot (1000 ms) were presented simultaneously. The target dot randomly appeared at $\pm 6^{\circ}$ or $\pm 12^{\circ}$ eccentricity. All stimuli were extinguished 1800 ms after dot and tone onset. A new trial started after 1300 ms.

A delayed trial started with the fixation of a central white cross on a black background for the duration of 1000, 1500, 2000 or 2500 ms at random. The fixation cross remained on the screen after the appearance of a peripheral target dot. The target dot randomly appeared at $\pm 6^{\circ}$ or $\pm 12^{\circ}$ eccentricity. After a delay of 800, 1000 or 1200 ms, a 440 Hz sine wave tone was presented for 50 ms while both fixation cross and peripheral target remained on for the remainder of the trial. A new trial commenced after 1300 ms.

The participant was instructed to fixate the central cross and to look towards the peripheral target dot as quickly and as accurately as possible whenever the tone was presented (prosaccade trials), or to look to the mirror position of the target dot as quickly and as accurately as possible whenever the tone was presented (antisaccade trials).

Altogether there were 144 trials (72 prosaccade and 72 antisaccade trials). The sequence of peripheral target presentations was pseudo-randomized. There were five practice trials before each block which were not included in the analysis.

Eye movement recording and analysis

Eye movements were recorded using electro-oculography. Eye movement recording and analysis have been described in detail elsewhere (Petrovsky et al., 2012). The dependent variables were latencies of pro- and antisaccade trials (time between tone appearance and saccade initiation of correct trials) and percentage antisaccade errors (the first saccade after appearance of the peripheral target was performed towards the target). The antisaccade error rate is calculated as the percentage

Table 1. Demographic, clinical and smoking characteristics

	Patients ($n=22$)		Controls ($n=26$)		
	Smokers	Non-smokers	Smokers	Non-smokers	p
n	12	10	14	12	0.96
Sex (m/f)	77/5	5/5	7/7	4/8	0.66
Age (yr)	33.33 (10.72)	37.60 (5.40)	31.29 (8.99)	31.17 (9.82)	0.33
Parental SES	12.34 (1.74)	15.53 (2.99)	14.61 (2.70)	13.81 (2.94)	0.06
Verbal IQ	103.67 (10.62)	121.30 (14.73)	103.57 (10.50)	112.83 (16.34)	0.006
Order of patch (n nicotine first/n placebo first)	7/5	6/4	4/10	7/5	0.30
Years of illness	9.33 (8.42)	10.30 (7.30)			0.78
Chlorpromazine equivalents	321.32 (241.40)	731.69 (466.45)			0.03
PANSS positive	11.83 (2.86)	12.10 (1.85)			0.80
PANSS negative	15.17 (7.04)	10.60 (2.91)			0.07
PANSS overall pathology	28.25 (8.97)	27.30 (5.52)			0.77
CDSS	4.75 (4.99)	4.00 (3.40)			0.40
Pack years	14.41 (14.88)		10.67 (6.63)		0.41
FTND score	6.33 (2.71)		3.00 (2.35)		0.003
Cigarettes/d	18.73 (8.45)		13.54 (6.15)		0.09

m, Male; f, female; SES, Socioeconomic status; FTND, Fagerström Test for Nicotine Dependence; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia.
Data represent means (S.D) unless otherwise specified.

of error trials over the total number of valid saccade trials (excluding e.g. eye-blink trials).

Statistical analyses

Statistical analyses were conducted using the software PASW Statistics 18 (SPSS Inc., USA). For the statistical analysis of nicotine effects on saccadic variables $2\times2\times2\times2\times2$ repeated-measures analyses of variance (ANOVA) were calculated with drug (placebo, nicotine) and delay (standard trial, delay trial) as within-subjects factors and psychosis (patients, controls), smoking (smokers, non-smokers) and order (nicotine/placebo, placebo/nicotine) as between-subjects factors. Order was included as a factor to account for possible practice effects and possibly unbalanced distribution of patch order across the subgroups. As our design is a factorial design with five factors, each factor having two levels, it is quite a complex design. Therefore, we present the results for each saccadic variable (antisaccade errors, antisaccade latency, prosaccade latency) separately to enhance readability. Main effects and simple interactions are presented first, followed by the higher-order interactions. Higher-order interactions (e.g. triple interactions) should be interpreted with caution as for subgroup analyses the statistical power is decreased and the risk of finding at least one spurious statistically significant result is increased. Finally, we also explored whether performance change scores (i.e. difference values: placebo data – nicotine data) were correlated with neuroleptic dose (i.e. chlorpromazine equivalents), PANSS scores, number of cigarettes/d, Fagerström Test for Nicotine Dependence (FTND) score and cotinine plasma level using Pearson's correlations. Greenhouse–Geisser correction of p-values was applied when sphericity was violated. The significance level of all statistical tests was set at $p<0.05$.

Results

Demographic, clinical and smoking characteristics

A total of 22 patients with psychosis (12 smokers and 10 non-smokers) and 26 controls (14 smokers and 12 non-smokers) participated in the study. Participants were matched regarding smoking status, sex, age and parental socio-economic status (Table 1). However, non-smoking patients exhibited a higher verbal IQ than smoking patients ($p=0.02$) and smoking controls ($p=0.01$), whereas non-smoking patients did not differ from non-smoking controls ($p=0.83$; Bonferroni-corrected *post hoc* comparisons). Smoking patients did not differ from smoking controls regarding pack years. However, smoking patients differed from smoking controls on the FTND score and patients also tended to smoke more cigarettes/d than controls (Table 1). Nineteen patients were diagnosed with schizophrenia, paranoid type (DSM-IV 295.3) and three were diagnosed with schizo-affective disorder (DSM-IV 295.7). All patients were out-patients and received treatment with atypical antipsychotics (six received quetiapine and/or risperidone, 10 received clozapine and/or amisulpride, five

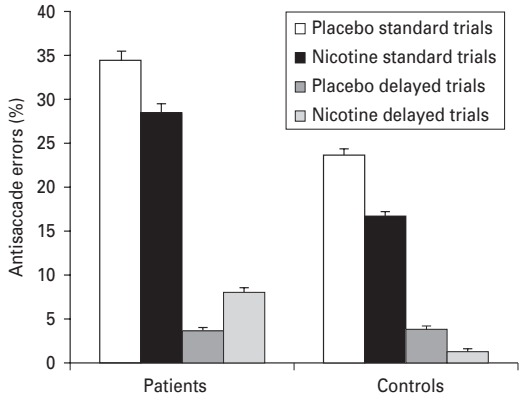

Fig. 1. Effects on antisaccade error rate in patients and controls (means ± S.E.). Schizophrenia patients made significantly more antisaccade errors than controls (main effect of psychosis, $p = 0.03$). Both patients and controls made fewer antisaccade errors in the delayed trials than in the standard trials (main effect of delay, $p < 0.0001$). Nicotine significantly reduced antisaccade error rate in the standard trials, but not in the delayed trials (drug × delay interaction, $p = 0.02$).

received olanzapine and/or aripiprazole, three received amisulpride and one received ziprasidone). The average dose of antipsychotic medication was 578.76 ± 486.01 mg/d chlorpromazine equivalents (Woods, 2003; Bazire, 2010) with non-smoking patients receiving on average a higher dose than smoking patients. Four patients additionally received the antidepressant citalopram. Patients exhibited low scores of positive and negative symptoms as well as low scores of overall pathology and depression (see Table 1).

Cotinine plasma levels

Cotinine data of 44 participants were available. In non-smoking participants, mean cotinine plasma levels were significantly higher for the nicotine session (16.43 ± 7.66 ng/ml) than for the placebo session (0.92 ± 2.18 ng/ml; $t_{18} = 8.66$, $p < 0.001$). Likewise, in smoking participants mean cotinine plasma levels were significantly higher for the nicotine session (167.27 ± 91.65 ng/ml) than for the placebo session (94.31 ± 81.50 ng/ml; $t_{23} = 7.72$, $p < 0.001$) indicating successful experimental manipulation.

Antisaccade errors

There was a significant main effect of psychosis ($F_{1,40} = 5.18$, $p = 0.03$, $\eta^2_P = 0.12$) indicating that schizophrenia patients made more antisaccade errors (19.02 ± 14.02%) than controls (13.79 ± 10.83%). There was a significant main effect of delay ($F_{1,40} = 107.36$, $p < 0.0001$, $\eta^2_P = 0.73$), but no significant psychosis × delay interaction ($F_{1,40} = 2.82$, $p = 0.10$, $\eta^2_P = 0.07$): both patients and controls made fewer antisaccade errors in the delayed trials than in the standard trials (see Fig. 1 and Table 2). We did not find a main effect of drug ($F_{1,40} = 1.34$, $p = 0.25$, $\eta^2_P = 0.03$), but we found a significant drug × delay interaction ($F_{1,40} = 5.56$, $p = 0.02$, $\eta^2_P = 0.12$) demonstrating that nicotine decreased antisaccade error rate in standard trials but not delayed trials (see Fig. 1). There were no significant psychosis × drug ($F_{1,40} = 0.54$, $p = 0.47$, $\eta^2_P = 0.01$) or psychosis × drug × delay ($F_{1,40} = 1.88$, $p = 0.18$, $\eta^2_P = 0.05$) interactions, indicating that nicotine enhanced antisaccade performance by decreasing antisaccade error rate in patients and controls equally. There was a trend for a main effect of smoking ($F_{1,40} = 3.03$, $p = 0.09$, $\eta^2_P = 0.07$): smokers tended to make more antisaccade errors (19.04 ± 14.28%) than non-smokers (12.82 ± 9.89%). There was no smoking × drug interaction ($F_{1,40} = 0.14$, $p = 0.71$, $\eta^2_P = 0.004$) and there was no significant smoking × drug × delay interaction ($F_{1,40} = 2.88$, $p = 0.10$, $\eta^2_P = 0.07$) indicating that smoking status did not influence the nicotine effect on antisaccade error rate. There were no main ($F_{1,40} = 0.0001$, $p = 0.99$, $\eta^2_P < 0.0001$) or interaction effects of order (all $p > 0.18$) on antisaccade error rate. There were no further higher order interactions for antisaccade error rate (all $p > 0.17$).

Antisaccade latency

There was no main effect of psychosis ($F_{1,40} = 0.63$, $p = 0.43$, $\eta^2_P = 0.02$) on antisaccade latency. There was a significant main effect of delay ($F_{1,40} = 572.14$, $p < 0.0001$, $\eta^2_P = 0.94$) demonstrating that all participants exhibited lower antisaccade latencies in the delayed trials compared to the standard trials (see Fig. 2 and Table 2). There was also a trend for a psychosis × delay interaction ($F_{1,40} = 4.21$, $p = 0.05$, $\eta^2_P = 0.10$) indicating that the control group benefited to a greater extent from the delayed condition (difference standard – delayed trials = 161.32 ms) than the patient group (difference standard – delayed trials = 135.83 ms). There was a main effect of drug ($F_{1,40} = 16.14$, $p = 0.0003$, $\eta^2_P = 0.29$): nicotine decreased antisaccade latencies (see Fig. 2). No drug × delay interaction was found ($F_{1,40} = 0.08$, $p = 0.78$, $\eta^2_P = 0.002$). The psychosis × drug interaction ($F_{1,40} = 2.74$, $p = 0.11$, $\eta^2_P = 0.06$) was not significant. There was no psychosis × drug × delay triple interaction ($F_{1,40} = 0.18$, $p = 0.67$, $\eta^2_P = 0.005$). There was no main effect of smoking ($F_{1,40} = 0.63$, $p = 0.43$, $\eta^2_P = 0.02$), but there was a significant smoking × delay interaction ($F_{1,40} = 6.97$, $p = 0.01$, $\eta^2_P = 0.15$). Non-smokers benefited from the delayed condition to a greater extent (difference standard – delayed trials = 192.61 ms) than smokers (difference standard – delayed trials = 127.61 ms). The smoking × delay × drug triple interaction tended towards significance ($F_{1,40} = 3.81$, $p = 0.06$, $\eta^2_P = 0.09$): nicotine tended to decrease antisaccade latencies in the delayed trials to a greater extent in smokers (difference placebo –nicotine = 31.75 ms) than in non-smokers (difference placebo – nicotine = 7.82 ms). The smoking × delay × psychosis triple interaction also tended towards significance ($F_{1,40} = 2.93$, $p = 0.09$, $\eta^2_P = 0.07$): non-smoking

Table 2. Saccadic performance

	Schizophrenia patients ($n=22$)				Controls ($n=26$)				All participants ($n=48$)			
	Standard trials		Delayed trials		Standard trials		Delayed trials		Standard trials		Delayed trials	
	Placebo	Nicotine	Placebo	Nicotine	Placebo	Nicotine	Placebo	Nicotine	Placebo	Nicotine	Placebo	Nicotine
Antisaccade error rate (%)	34.4 (22.9)	28.4 (20.4)	3.7 (5.1)	8.0 (12.8)	23.7 (15.2)	16.7 (13.5)	3.9 (6.5)	1.2 (3.5)	29.1 (19.1)	22.6 (17.0)	3.8 (5.8)	4.6 (8.2)
Antisaccade latency (ms)	361.09 (56.69)	353.78 (64.90)	225.93 (77.31)	216.52 (61.70)	399.00 (66.23)	362.73 (55.62)	241.02 (52.73)	210.62 (34.52)	380.05 (61.46)	358.26 (60.26)	233.48 (65.02)	213.57 (48.11)
Prosaccade latency (ms)	283.65 (71.67)	289.43 (62.86)	230.97 (61.88)	222.53 (58.89)	310.10 (46.36)	302.12 (44.56)	232.81 (43.05)	219.38 (38.57)	296.88 (59.02)	295.76 (53.71)	231.89 (52.47)	220.96 (48.73)

Data represent means (S.D.).

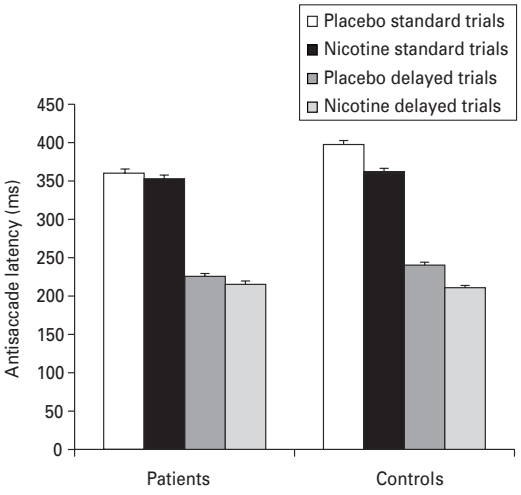

Fig. 2. Effects on antisaccade latency in patients and controls (means ± S.E.). Schizophrenia patients did not differ from controls regarding antisaccade latency (no main effect of psychosis, $p=0.43$). Both patients and controls exhibited shorter antisaccade latencies in the delayed trials than in the standard trials (main effect of delay, $p<0.0001$). Nicotine significantly reduced antisaccade latencies (main effect of drug, $p=0.0003$), but there was no drug × delay interaction ($p=0.78$). The drug × psychosis interaction was not significant ($p=0.11$).

schizophrenia patients tended to benefit more from delayed trials than smoking patients and the control group. There was a trend for a main effect of order on antisaccade latency ($F_{1,40}=3.26$, $p=0.08$, $\eta^2_P=0.07$) and there was a significant drug × order interaction ($F_{1,40}=22.83$, $p<0.0001$, $\eta^2_P=0.36$) indicating that those participants who received the nicotine patch at session two exhibited a decreased antisaccade latency. There were no further higher order interactions for antisaccade latency (all $p>0.76$).

Prosaccade latency

There was no main effect of psychosis ($F_{1,40}=0.27$, $p=0.61$, $\eta^2_P=0.007$) indicating that schizophrenia patients and controls did not differ in prosaccade reaction time. There was a significant main effect of delay ($F_{1,40}=87.35$, $p<0.0001$, $\eta^2_P=0.69$): prosaccade latencies were shorter in delayed trials than in standard trials. However, there was no psychosis × delay interaction ($F_{1,40}=1.62$, $p=0.21$, $\eta^2_P=0.04$) indicating that a delay decreased prosaccade latencies in patients and controls equally. There was no main effect of drug ($F_{1,40}=1.87$, $p=0.18$, $\eta^2_P=0.05$) or drug × delay interaction ($F_{1,40}=1.13$, $p=0.30$, $\eta^2_P=0.03$). No main effect of smoking ($F_{1,40}=0.88$, $p=0.35$, $\eta^2_P=0.02$) or smoking × drug interaction was found ($F_{1,40}=0.91$, $p=0.34$, $\eta^2_P=0.02$). There was a trend for a main effect of order ($F_{1,40}=3.17$, $p=0.08$, $\eta^2_P=0.07$) on prosaccade latency and there was a significant drug × order interaction ($F_{1,40}=11.38$, $p=0.002$, $\eta^2_P=0.22$) indicating that those participants who received the nicotine patch at session two showed a decreased prosaccade reaction time. It is

very likely that this interaction reflects a practice effect from session one to session two. There were no higher order interactions effects with order (all $p > 0.32$) and no further higher order interactions were found for prosaccade latency (all $p > 0.78$).

Correlations with performance change scores

With the finding that nicotine decreased antisaccade error rate in the standard trials, we investigated whether the level of habitual smoking was related to this effect. In the entire sample, number of cigarettes/d was not significantly correlated with performance change scores (i.e. placebo – nicotine) of antisaccade error rate in standard trials ($r = 0.21$, $p = 0.33$). Likewise, there was no such significant correlation in the subsample of patients ($r = 0.26$, $p = 0.44$) nor in the subsample of controls ($r = 0.20$, $p = 0.49$). FTND scores also were not correlated with performance change scores ($r = 0.09$, $p = 0.67$) and there was no significant correlation in either the subsample of patients ($r = 0.29$, $p = 0.36$) or in the subsample of controls ($r = -0.11$, $p = 0.71$). In addition, we evaluated whether performance change score was related to neuroleptic dose (i.e. chlorpromazine equivalents) and PANSS scores in patients. Chlorpromazine equivalents were not significantly correlated with performance change score ($r = 0.01$, $p = 0.97$). PANSS scores were also not significantly correlated with performance change score (all $r < 0.03$, all $p > 0.88$). Finally, we tested whether there was a correlation between cotinine plasma levels and performance change scores. In the entire sample, cotinine plasma level was significantly positively correlated with performance change score of antisaccade error rate in standard trials ($r = 0.36$, $p = 0.02$). This correlation was significant in the subsample of patients ($r = 0.44$, $p = 0.048$), but not in the subsample of controls ($r = 0.25$, $p = 0.24$).

Discussion

In the present study we replicated the finding of increased antisaccade error rates in schizophrenia patients compared to controls indicating worse antisaccade performance in schizophrenia patients. However, we did not find longer antisaccade latencies in schizophrenia patients. Possibly, this lacking group difference is due to the antisaccade task design with intermixed standard and delayed trials: Reuter et al. (2005) who used a very similar design also failed to find significantly longer antisaccade latencies in the patient group. Similarly to Reuter et al. (2005, 2007), we also found a performance-enhancing effect of delay: both schizophrenia patients and controls made significantly fewer antisaccade errors and exhibited shorter antisaccade latencies in the delayed trials than in the standard trials. We also employed a block of prosaccades as a control condition. As for the antisaccade condition, we found a significant latency-reducing effect of delay indicating that elongated fixation also improved prosaccadic eye movements. We did not find any effects of nicotine on prosaccade performance indicating that nicotine specifically enhanced performance in the more demanding antisaccade task.

The main focus of the present study was to examine effects of nicotine on antisaccade performance. The first main finding was that nicotine improved antisaccade performance in schizophrenia patients and controls equally, i.e. we did not find interaction effects with psychosis status. Nicotine significantly reduced antisaccade error rates in standard trials, but not in delayed trials. This error-reducing effect of nicotine replicates findings from previous studies in which standard antisaccade paradigms (i.e. without a temporal delay) were used (Depatie et al., 2002; Larrison-Faucher et al., 2004) and extends them by suggesting that performance in delayed antisaccades is not influenced by nicotine. Possibly, nicotine selectively enhanced inhibition of reflexive saccades in standard trials and did not influence delayed trials as the effect of delay may already have supported inhibition sufficiently. As the effect of delay was very pronounced in our study, our participants were probably already performing at maximum; not allowing further improvement by nicotine. Thus, future studies are needed to investigate which component of antisaccade performance (i.e. inhibition or saccade generation) is enhanced by nicotine.

Furthermore, nicotine reduced antisaccade latencies in patients and controls regardless of trial type (i.e. trial with or without delay). Two studies in healthy participants also demonstrated that nicotine decreased antisaccade reaction times (Rycroft et al., 2007; Ettinger et al., 2009), whereas the study by Larrison-Faucher et al. (2004) merely found a trend for nicotine to reduce antisaccade latencies and the study by Depatie et al. (2002) did not find an effect of nicotine on antisaccade latency. These inconsistent results regarding antisaccade latency might indicate that antisaccade error rate is the parameter which is more sensitive to the effects of nicotine. In the present study, we also found a practice effect for antisaccade latencies. The significant interaction of the factors drug and order indicated that the subgroup which had nicotine at session two performed best. It is very likely that this was due to the combination of a practice effect from session one to session two and a nicotine effect.

An important finding is that smoking status did not influence nicotine effects on antisaccade performance indicating an equal procognitive effect of nicotine in smokers and non-smokers. So far, the published studies on antisaccade performance and nicotine treatment in schizophrenia patients (Depatie et al., 2002; Larrison-Faucher et al., 2004) only tested participants who were smokers. Therefore, our results favour a genuine nicotine effect instead of a simple relief-from-withdrawal phenomenon. A study by Ettinger et al. (2009) in healthy participants administered nicotine and placebo on two

separate occasions and tested light-to-moderate smokers and non-smokers with the antisaccade task. Nicotine significantly reduced antisaccade latencies both in smokers and in non-smokers (Ettinger et al., 2009). In addition, the amount of the nicotine-induced reduction in antisaccade latency in smokers was comparable to the reduction in antisaccade latency caused by nicotine in non-smokers (Ettinger et al., 2009). The results of Ettinger et al. (2009) also support the idea that nicotine is effective in improving antisaccade performance both in smokers and non-smokers. Finally, the clinical trial by Hong et al. (2011) demonstrated that the $\alpha 4\beta 2$ nAChR agonist varenicline reduced antisaccade error rate in patients with schizophrenia regardless of smoking status. The results of Hong et al. (2011) further underline the notion of a genuine procognitive effect of cholinergic modulation on antisaccade performance.

Limitations of the present study include the relatively small sample size and the fact that the smoking participants were deprived of smoking (overnight abstinence) when they received nicotine treatment. This feature of the design makes it difficult to disentangle genuine nicotine effects from relief-from-withdrawal in the subsample of smoking participants. Therefore, future studies might want to opt for a minimum amount of deprivation such as 2 h as suggested by Heishman et al. (2010). Furthermore, future studies should assess withdrawal symptoms, e.g. with the Cigarette Withdrawal Scale (Etter, 2005).

In conclusion, the present findings indicate that beneficial effects of nicotine on antisaccade performance are not confined to smoking schizophrenia patients. Rather, the present results suggest an equal procognitive effect of nicotine on antisaccade error rate in smokers and non-smokers. More generally, the present study suggests that the antisaccade paradigm is well suited as a neurocognitive biomarker for the investigation of the effectiveness of cholinergic substances in future clinical trials.

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Statement of Interest

None.

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